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Comparison of surveillance *vs* Aortic Endografting for Small Aneurysm Repair (CAESAR) Trial: Study Design and Progress

CAESAR Trial Collaborators*

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Objective. *The CAESAR Trial aims to assess the outcome of endovascular repair (EVAR)* vs *surveillance of small abdominal aortic aneurysms (AAA) with maximum diameter of 4.1–5.4 cm on computerised tomography (CT) scan.*
Design. *Patients between 50 and 80 years of age, with small AAA, anatomically suitable for EVAR, are randomly allocated to early EVAR or surveillance. The primary outcome measure is survival. Secondary endpoints include: Aneurysm-related deaths (defined as any death caused directly or indirectly by rupture or endovascular/open aneurysm repair), AAA rupture, peri-operative or late complications, conversion to open repair, complications associated with delayed treatment including loss of treatment options, AAA growth rates and quality of life. Target recruitment is 740 patients to show that early EVAR is associated with a 15% survival benefit at 54 months.*
Progress. *Randomisation started in September 2004. By the end of April 2005, 86 patients had been enrolled by 10 active European centres. Completion of recruitment is expected for September 2006 and publication of the results in mid 2007.*

Keywords: Abdominal aortic aneurysm; Small aneurysm; Endovascular repair; Randomised controlled trial; Surveillance.

Introduction

The strongest known predictor of rupture and rupture-related death of abdominal aortic aneurysm (AAA) is the maximum diameter of the aneurysm. There is considerable historical evidence that elective surgical repair improves survival of patients with large AAA.[1,2] In contrast, there is only limited evidence and much debate on the best management of risk for patients with small AAA (4.1–5.4 cm).[3–8] The rupture rate for aneurysms smaller than 5.5 cm under surveillance is lower than that of larger aneurysms. However, recent enthusiasm surrounding endovascular repair of aortic aneurysm (EVAR) has increased pressure to extend the indications for repair to smaller aneurysms, because of reduced major morbidity and stress response of EVAR compared to open surgery.

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Previous Publications and Rationale

Treatment of AAA is appropriate when cumulative risk of rupture exceeds risk of repair. For the common low risk patient with AAA <5.5 cm, the balance of risks between treatment and no treatment may not be easy. Two large randomized controlled trials (RCT), one British and one American (UK Small aneurysm trial and ADAM trial) have attempted to address this topic by enrolling over 2000 patients randomized to early treatment *vs* surveillance without reaching any strong conclusions.[3,4] The only evidence from the results of both RCTs was that the critical issue for patients with small AAA is to define 'when' and not 'if' to treat. The risks to be balanced are those of early treatment with respect to those of delayed treatment. Because the natural history of an aneurysm is that of continued expansion, it was inevitable that about 70% of patients with small AAA in the surveillance group required treatment during the 5-year study period, at a similar rate in both RCTs.

Both RCTs concluded that surveillance was relatively safe and delayed treatment yielded similar 5-year survival rates oft about 66%. However, it also might be noted that

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- these results could have been obtained by a combination of clinical follow up, careful medical management and strict ultrasound surveillance, which might be difficult to achieve in the common practice outside RCT,
- even with a high rate of intervention in a patient population willing to undergo frequent and reliable surveillance, the rupture rate of small aneurysm may still be greater than 2% per year in some subgroups of the patient population (e.g. females),
- long-term results of one of the two studies (the UK trial) might indicate a benefit of early treatment as 8-year mortality in the early surgery group was 7.2% points lower than that in the surveillance group. Patients with long life expectancy benefit the most from early surgery.[9]

An additional point of concern is the applicability rate of EVAR, which might be reduced in patients under surveillance whose AAA is growing. There is increasing knowledge both from registries and from large single centre series showing that both feasibility and long-term outcomes of EVAR appear to be much worse for larger aneurysms. Two years after EVAR in the Cleveland Clinic series, 6.1% of patients with AAA that measured 5.5 cm or larger had aneurysm-related deaths and 8.2% required conversion to open repair, compared to 1.5 and 1.4% respectively, of those with aneurysms measuring less than 5.5 cm. Similarly, the 4-year post-operative rupture rate in the EUROSTAR registry was 10% for AAA measuring 6.5 cm or more in diameter compared to 2% for smaller aneurysms.[10,11]

In the 'real word' this uncertainty among optimal strategies for treatment of small AAA translates in a high rate of surgical treatment based on arbitrary indication and personal opinion. Data from large registries and multicenter experiences on AAA show that worldwide AAA repair (either endovascular or open) is performed on aneurysms with a diameter range from <4 to over 10 cm with variable results. Forty-five percent of the EUROSTAR patients and nearly 60% of the Cleveland patients who were treated with endovascular repair had aneurysms smaller than 5.5 cm.[10,11]

Therefore, we conclude that endovascular repair may represent the treatment of choice for small AAAs. To test this hypothesis, a randomized trial of early endovascular repair *vs* surveillance is being conducted.

Materials and Methods

The Comparison of surveillance *vs* Aortic Endografting for Small Aneurysms Repair study (CAESAR) is a multicentre randomised trial designed to compare EVAR *vs* surveillance with ultrasonography and computed tomography (CT) in the treatment of aortic aneurysms between 4 and 5.5 cm in diameter.

Purpose and objectives of the CAESAR study

The study includes patients with small AAA (diameter 4.1–5.4 cm defined by computed tomographic scan) suitable for EVAR. The purpose is to compare endovascular repair *vs* surveillance and, eventually delayed treatment, with respect to patient survival, AAA rupture and AAA-related death risks.

The primary study endpoint is mortality from any cause.

Secondary endpoints include: Aneurysm-related deaths (defined as any death caused directly or indirectly by rupture or endovascular/open aneurysm repair), AAA rupture, peri-operative or late complications, conversion to open repair, complications associated with delayed treatment including loss of treatment options, AAA growth rates and health related quality of life.

All complications are combined in one comprehensive outcome. Complications are assessed at 30 days (peri-operative) and during the entire length of follow-up and defined according to the SVS/AAVS reporting standards.[12] A secondary cost analysis will be performed according to: Cost of the graft, operating time, length of hospital stay including intensive care admission, follow-up visits with imaging examinations, need and number of reinterventions, and blood transfusion.

Participants

Entry criteria

All standard-risk patients with an AAA eligible for EVAR can be considered for participation in the CAESAR trial. Required entry criteria are shown in Table 1.

Centre selection

Centres compliant with endovascular/open aortic repair and who have experience beyond the learning curve for endovascular AAA repair are accepted in the trial. This means that, to participate in the trial, each centre is required to have performed at least 50 AAA endovascular procedures, have a minimum annual

Table 1. Entry criteria for CAESAR study

Inclusion criteria
Patients of 50–80 years of age
Non symptomatic infrarenal AAA of 4.1–5.4 cm in diameter measured by CT performed within 3 months before randomization
Adequate infrarenal aortic neck (length $\geq$15 mm diameter $\leq$30 mm) and other anatomical configurations suitable for EVAR
Patients have a life expectancy of at least 5 years
Signed informed consent
Exclusion criteria
Ruptured or symptomatic AAA
AAA maximum diameter $\geq$5.5 cm
Suprarenal or thoracic aorta aneurysm of more than 4.0 cm
Patient unsuitable for administration of contrast agent
Severe heart, lung, liver or renal disease (serum creatinine $\geq$3 mg/dl)
Need for adjunctive major surgical or vascular procedures within 1 month
High likelihood of non compliance with follow-up requirements

volume of 50 AAA open or endovascular repairs and must have provided a track record of all the endovascular/open AAA procedures performed during the last 2 years.

Furthermore, the participants in each centre must agree to submit all eligible patients to randomisation, to adhere to the guidelines of the trial until it is concluded, to guarantee strict adherence to follow-up and to ensure high-quality CT scan and ultrasonography studies.

Centres must have obtained Human Ethics Committee approval from their institutions for the conduct of the randomised trial prior to enrolling patients.

Imaging

The criterion for entry into both arms is an aneurysm diameter measuring 4.1–5.4 cm on CT scan. Because reproducibility differences between duplex ultrasound and CT scanners can lead to significant variation in AAA diameter, CT measurements are mandatory to determine the diameter of the aneurysm and the suitability for EVAR before randomisation. CT examinations are performed with contrast agent and slice reconstruction at no more than 5 mm intervals.

The diameter of the aneurysm is defined on CT scan as the maximum external cross-sectional measurement in any plane but perpendicular to the vessel axis. Measurements are reviewed centrally. The core laboratory for analysis of the imaging data is the Vascular Surgery Unit, Azienda Ospedaliera, University of Perugia, Italy.

Randomisation and management

A patient who meets the entry criteria and is willing to participate in the study is included after signing the informed consent form.

All anonymised records of patients with AAA between 4 and 5.5 cm in diameter not included in the trial are kept in a separate database. It is of particular importance that patients found to be unsuitable for the Caesar study are recorded. Reasons for exclusion are recorded in order to determine what proportion of AAA patients are anatomically suitable for EVAR.

Randomisation

Randomization was designed with equal probability of assignment to either of the two groups by means of a computer-generated random-number list. After eligibility is verified and the patient is considered suitable for the study, assignment is made using a computerized randomization table accessible via the internet to authorized investigators at each centre (www.caesarstudy.com). The treatment allocated is available immediately to the trial investigator, surgeon and patient. Since many variables are likely to be specific to each participating centre (i.e. team experience, case load, etc.), randomisation is stratified by centre.

Treatment groups and follow-up

Endovascular repair

For patients randomized to early endovascular treatment, the repair has to be carried out as soon as possible. Specific procedural details are left to the discretion of the surgeon.

Before discharge, a color duplex ultrasound and abdominal plain X-ray (double projection) are required. Clinical and imaging follow-up are then performed at 30 days and every 6 months thereafter. Double projection plain abdominal X-rays are also used to follow patients after EVAR to assess stent integrity. CT scan with slice reconstruction at 5 mm intervals or less is performed annually.

All adverse events occurring after randomisation, before or after treatment, (e.g. graft migration, disconnection, persisting endoleak, aneurysm growth,

need for secondary procedures, etc.) are assessed, documented, treated if necessary and recorded.

Surveillance group

Patients who are assigned to the surveillance arm of the trial are seen every 6 months throughout the study. Follow-up assessment includes clinical, ultrasonography evaluations and annual CT scan. In patients under surveillance and with creatinine levels of 2 mg/100 ml or more, the use of contrast agent is not mandatory and left to the discretion of the investigator.

Ultrasonography is not used to define aneurysm baseline diameter but only to monitor aneurysm size and to assess achievement of threshold criteria, that will need CT scan confirmation.

Surveillance visits continue until either the patient dies, the trial ends, or surgery is considered and performed. Surgery is considered only when the aneurysm grows to 5.5 cm, rapidly increases in diameter (>1 cm/year), or becomes symptomatic. Patients in the surveillance group who meet one or more threshold criteria to be converted to surgical repair will be evaluated to assess the persistence of anatomical suitability for EVAR.

Any patient in the surveillance group who requires repair during follow-up is followed until completion of the trial. Fig. 1 shows the protocol for enrolled patients.

Health related quality of life is assessed in both groups at 6-month intervals with short-form 36-items (SF-36) questionnaire administration.[13]

Device

The CAESAR study has been funded to use a single device in the trial: The Zenith® AAA Endovascular Graft (William Cook Europe, Bjaeverskov, Denmark). This also guarantees homogeneity of the results for all EVAR patients included in the study. Any configuration is allowed, including tube, bifurcated and mono-iliac devices. Use of ancillary components such as extensions is left to the discretion of the investigator performing the procedure. A grant from William Cook Europe, Bjaeverskov, Denmark will support the expenses for the organization of the study. However, the design and the study itself are conducted independently.

Study population and sample size

Required sample size was estimated at 740 patients (i.e. 370 patients per group) to detect a difference in survival rates between the EVAR and control group by the log-rank test with conventional 0.80 power and 5% significance.[14] The intention is to demonstrate that mortality rate after 54 months of patients with small AAA treated early by EVAR is 15% lower than that of patients in the surveillance group. Survival rates at 12, 36 and 54 months for the surveillance group were assumed to be 0.98, 0.83 and 0.68% as reported in The United Kingdom Small Aneurysm Trial Participants.[3] The corresponding figures for the EVAR group used for sample calculation were 0.98, 0.88, and 0.83% at 12, 36 years and 54 months follow-up, respectively, and were obtained from cases (small AAAs undergone endovascular treatment) treated at the coordinating centre. Sample size was calculated taking into account that risk difference was not constant during follow-up, thus, the hazard ratio was assumed to be about 1, 0.7 and 0.6 at 12, 36 and 54 months follow-up, respectively. For sample size calculations we made additional assumptions: A uniform rate of recruitment over a 2-year period, an additional follow-up at 3 years, and the proportion lost to follow-up to be as low at 3%.

Statistical analysis

The outcome analyses are conducted according to the intention-to-treat principle. STATA Statistical package will be used for analyses (Stata Corp. Stata Statistical Software, release 8.0. College Station, TX: Stata Corporation, 2003) and performed by the Study Statistician.

Cumulative survival curves will be used and the differences between the treatment groups will be evaluated by log-rank test. Estimates of risk in the surveillance group compared to the EVAR group and 95% confidence intervals are calculated with the use of the Cox proportional hazards model or parametric models. The survival model is adjusted for potential confounding variables, which are expected to influence mortality. These include age, gender, history of ischemic heart disease, chronic obstructive airways disease. Absolute risk, relative risk and number need to treat (NNT) are calculated as estimates of risk. *P* values are two-tailed and are obtained with the chi-square tests or *t*-test.

Current status

Recruitment began in September 2004, and by the end of April 2005 a total of 86 patients had been included in the CAESAR trial by 10 active randomising centres. Other European Centres recently received Local Ethical Committee approval to actively randomise. The CAESAR Data Monitoring Committee has

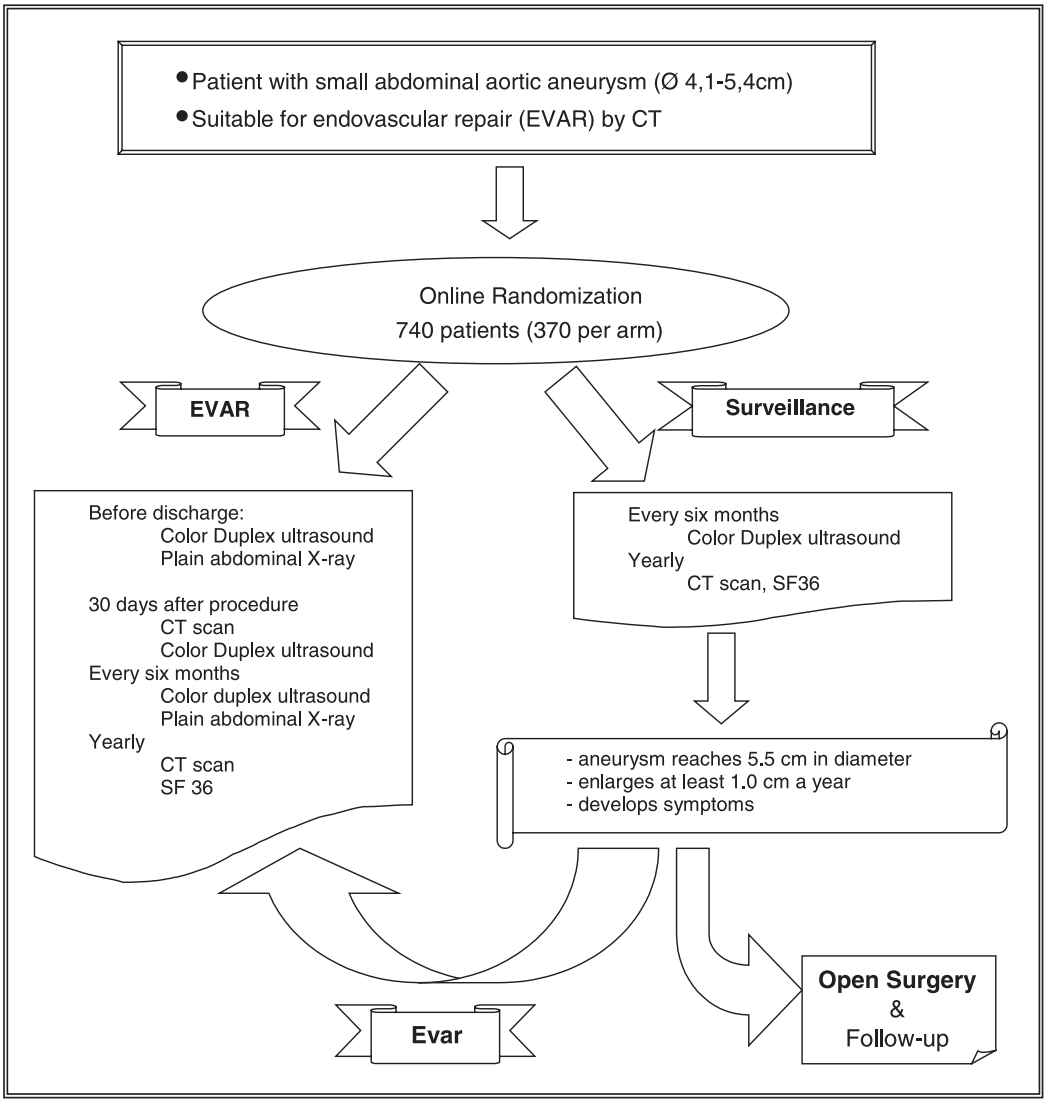

Fig. 1. Flow chart for patients enrolled into CAESAR Trial.

recommended that recruitment into the trial is completed by the end of August 2006. In order to accrue sufficient patient years of follow-up, a minimum of 1 year of follow-up is required per patient and on this timescale we might expect to publish the results of the trial in mid 2007. However, a final publication date has not been decided and further long-term follow-up after EVAR might still be required before a formal analysis is performed.

Conclusions

In this era of endovascular expansion, stent grafting for small AAA has been reported in several non-randomised trials with promising results.[7,8,10,11,15] Similarly, there are supporting data that surveillance and delayed treatment could be a safe choice for patients with small AAA. However, these results were based on open surgical treatment with a higher perioperative mortality rate than endografting.[7,16] The high re-intervention rate reported after endografting can make the cost effectiveness of this procedure unfavourable in patients with long life expectancy. On the other hand, patients with small aneurysms usually have a more favourable anatomy and the operation may be more durable lowering the need of reintervention. These aspects will be clarified by this study.

The CAESAR trial has been launched to answer the question 'Can early endovascular repair decrease the risk of death in patients with abdominal aortic aneurysm between 4 and 5.5 cm in diameter?' The trial will attempt to provide scientific evidence on the merits of endovascular repair of small AAAs. Patient

survival, AAA rupture and AAA-related death risks will be monitored. The normal practice of collaborating vascular specialists is studied, and appropriate follow-up schedule will be given to all trial patients.

Appendix A. Study Organization

No sponsor supports the design and plan of the study that was implemented by the Vascular Surgery Center in Perugia, the Coordinating Centre of the trial. This is the 'working' group of the study and is concerned principally with day-to day-operations. This group meets as often as necessary to deal with the wide range of problems relating to the study, e.g. eligibility, measurements criteria, adherence to the protocol, outcome events.

The Coordinating Centre meets periodically with other participating investigators and organizes periodic workshops to keep the participating centres actively involved and fully informed about the ongoing status of the study. This should avoid low patients accrual, high cross-over rates and incomplete follow-up. Regular visits by monitoring staff are planned in each center to assess the regularity of the study and to ensure uniformity of measurements, data collection and coding procedures. The Coordinating Centre also is responsible for the core-lab CT scan reassessment of patients enrolled in the study.

The Steering Committee, which includes a vascular specialist committee, is the policy- and decision-making body of the study and has the final responsibility for the conduct and the reporting of the trial. The Steering Committee receives regular reports from the Coordinating Centre concerning all information on the ongoing study (recruitment rate, adherence to protocol, cross-over, etc).

The Monitoring Committee ensures the proper conduct of the trial, assesses the ethical aspects and monitors the safety of the trial based on the reports of the Steering Committee. The Monitoring Committee will be responsible for reviewing the interim analysis and, if necessary, implementing the study stopping rule.

An Adverse Events Committee will convene as needed to adjudicate whether or not serious adverse events are related to the use of the device and/or the procedure.

Appendix B. Participants of the CAESAR Study†

Piergiorgio Cao, MD (Principal Investigator), Department of Vascular Surgery, Policlinico Monteluce, Perugia, Italy; Enrico Vecchiati, MD, Dipartimento di Chirurgia Vascolare Azienda Ospedaliera S.M. Nuova Reggio Emilia, Italy; Francesco Mascoli, MD, Dipartimento di Chirurgia Vascolare, Ospefdale S. Anna, Ferrara, Italy; Roberto Troiani, MD, Unità di Chirurgia Vascolare, Azienda Ospedaliera di Carrara, Carrara, Italy; Vicente Riambau, MD, Institute of Cardiovascular Diseases, Hospital clinic, University of Barcelona, Barcelona, Spain; Malgorzata Szostek, MD, Klinika Chirurgii Ogolnej i Chorob Klatki Piersiowej Warszawa, Poland; Jan Brunkwall, MD, Department of Vascular Surgery, Koeln Universitaet, Koeln, Germany; Dierk Scheinert, MD, Herz Zentrum, Universitaet Leipzig, Leipzig, Germany; Giovanni Torsello, MD, Klinik für Gefaesschirurgie, St Franziskus Hospital, Muenster, Germany; Marek Maruszynski, MD, II Klinika Chirurgii Ogolnej, Onkologicznej i Naczyniowej Wojskowy Instytut Medyczny, Warszawa, Poland; Volker Ruppert, MD, Department of Vascular Surgery, Ludwig Maximilians University, Munchen, Germany; Stefano Michelagnoli, MD, U.O. Chirurgia Vascolare, Nuovo Ospedale S. Giovanni di Dio, Firenze, Italy; Jacek Szmidt, MD, Naczyniowej I Transplantacyjnej Akademii Medycznej, Warsawa, Poland; Carlo Pratesi, MD, Department of Vascular Surgery, Università degli Studi di Firenze, Italy.

† Listed in the number of enclosed patients or the timing of adhesion order.

Appendix C. Data Monitoring Committee

Peter Bell, Chairman, Leicester, UK; Hajo von Bockel Leiden, The Netherlands; Paolo Fiorani, Rome, Italy, Krassi Ivancev, Malmö, Sweden.

Appendix D. Steering Committee

Piergiorgio Cao (Principal Investigator), Perugia, Italy; Fabio Verzini, Perugia, Italy; Paola De Rango, Perugia, Italy; Carlo Setacci, Siena, Italy; Vincent Riambau, Barcelona, Spain; Jan Brunkwall, Koeln, Germany.

Appendix E. Adverse Events Committee

Gianbattista Parlani, Perugia, Italy; Giovanni Torsello, Münster, Germany.

Note added in proof

Recent insights from randomised studies in EVAR vs Open Repair, the EVAR 1 Trial including subjects with

AAA larger than 5.5 cm and the DREAM Trial for AAA > 5 cm, seem to support our hypothesis[17,18].

EVAR 1 Trial showed in fact an anatomic suitability rate of 54% in potential candidates for enrolment, with a wide variety among different centers. Mid-term results highlighted a significant reduction in AAA-related death rate after EVAR compared to OR, starting from a 4% immediate postoperative advantage that persisted during follow-up (aneurysm-related death estimates at 4 years: 4% vs 7%. This advantage was not present in the EVAR 2 trial, which included patients unfit for open repair and randomised either in early EVAR or surveillance, suggesting that older patients with multiple comorbidities and at high operative risk are not going to benefit from intervention[19]. Therefore an early endovascular intervention, at a stage when the AAA is smaller, might suit a wider patient population with lower operative risk and hopefully better results.

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